REMARKS

This Supplemental Amendment is submitted in reply to the comments of the Advisory Action of December 9, 2009.

Status of the Claims

Claims 1, 6, 7, 12, 14-16, and 19 are currently pending and under examination. Claims 2-5, 8-11, 13, 17, and 18 have been canceled without prejudice or disclaimer of the subject matter claimed therein. The pending claims are allowable for the reasons noted below and otherwise of record.

Amendments to the Claims

Claims 1 and 19 have been amended for formalities.

The amendments to the claims do not introduce prohibited new matter.

Rejection Under 35 U.S.C. § 112, First and Second Paragraph

A. The Advisory Action of December 9, 2009 indicated that claims 1 and 19 would be rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite.

The Advisory Action indicated that the claims were unclear as to whether the type III AFP produced in a pmt1 and/or pmt2 deficient yeast was compared to glycosylated type III AFP or any glycosylated AFP. Without acquiescing to the merits of the comments, Applicants have amended the claims. It is believed that the amendments have overcome the basis for this alleged rejection.

B. The Advisory Action of December 9, 2009, further indicated that claims 1, 6-7, 9, 12, 14, 15, and 19 would continue to be rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to enable the claimed invention.

The Advisory Action alleges that the claims are unlimited in how pmt1 and/or pmt2 deficiency is achieved and that the claims may further encompass glycosylation deficiency through non-disclosed measures. The Advisory Action, however, fails to illustrate how one skilled in the art is not enabled by the claimed invention to obtain a pmt1 and/or pmt2 deficient

yeast. Applicants have previously listed a multitude of ways in which expression of pmt1 and/or pmt2, or for that matter expression of genes in general, can be altered. The Advisory Action has not refuted that and even notes that Ng discloses a method known in the art, but continues to allege that possible other methods exist to render a yeast deficient in pmt1 and/or pmt 2 expression. Applicants respectfully submit that the unlimited ways to obtain a pmt1 and/or pmt2 deficient yeast confirms that the specification provides sufficient guidance to practice the claimed invention. Accordingly, the invention is enabled.

Applicants submit that achieving pmt1 and/or pmt2 deficiency is well known in the art. Down-regulating expression of a protein in a yeast organism, particularly *S. cerevisae*, is very common, even to the most basic biologist. The sequences of pmt genes are disclosed in the art. Down regulation of pmt genes, and for that matter all known genes in *S. cerevisae*, can be achieved through knockout of the genes, or through targeting the mRNA to inhibit protein expression. Down regulation of genes can also be achieved through introducing a different promoter in front of the gene, so that an agent can bind to the promoter and inhibit/allow expression. One skilled in the art would not require undue experimentation to achieve a pmt deficient yeast. Applicants believe that one skilled in the art readily understands and can practice the invention as claimed. Accordingly, Applicants believe that it does not require undue experimentation to practice the claimed invention.

Rejection Under 35 U.S.C. § 103(a)

The Advisory Action also states that the claims would continue to be rejected under 35 U.S.C. § 103(a) as allegedly being obvious under Chapman (WO 97/02343) ("Chapman") in view of Ng (U.S. Patent Application Publication 2002/0068325) ("Ng") and Gentzsch (FEBS Lett 377: 128-130, 1995) ("Gentzsch 1").

Applicants have submitted references disclosing that type III AFP in wild type yeast are fully functional. Applicants have submitted references that demonstrate that one skilled in the art cannot predict what altering glycosylation will do to the function of a protein. As shown in the previously submitted references, it is not predictable as to which pmt enzymes or combinations thereof will affect glycosylation of a protein. Applicants have submitted a declaration under 37 CFR 1.132 by the inventor of both the claimed invention and of the primary

reference explaining how the claimed invention is non-obvious over the discovery of the type III AFP. The Advisory Action alleges that given the teachings of Ng, one of skill in the art at the time of the invention would be motivated to modify the reference of Chapman to use the expression host of Gentzsch. However, the Advisory Action has not cited any art that discloses to one skilled in the art how to predict which pmt enzymes will glycosylate a particular protein. The Advisory Action has not cited any art that discloses how to predict whether glycosylation has a positive or negative effect on protein function when expressed in yeast. The Advisory Action has cited no art that discloses how one skilled in the art, faced with a fully functional protein expressed in yeast, would predict that its function would be improved with less glycosylation.

Applicants submit that no evidence has been presented to rebut Applicants prior response. Applicants point out that the enablement rejection alleges that one skilled in the art could not achieve a pmt deficient yeast, yet the present rejection alleges that it would be obvious for one skilled in the art to arrive at the claimed invention.

In summary, Applicants have demonstrated that:

1. At the time of the present invention, one skilled in the art could not predict which enzymes would be responsible for glycosylating the type III AFP. The Declaration of Dr. Chapman refers to a reference of Gentzsch (Glycobiology 7: 481-486, 1997) ("Gentzsch 2", the author of Gentzsch 2 is the same as that of the cited Gentzsch 1 reference). Gentzsch 2 discusses the problems in attempting to manipulate the glycosylation of a protein in yeast. Gentzsch 2 discloses that the selection of one particular pmt enzyme is often ineffective in manipulating the glycosylation, and often 2 or 3 pmt enzymes will have to be affected. The Gentzsch 2 reference discloses that there is no way of predicting which pmt enzyme or combination of enzymes needs to be targeted for manipulating the glycosylation of a desired protein. It should be noted that Gentzsch 2 was published later than Gentzsch 1, and Gentzsch 2 particularly states that one skilled in the art has absolutely no guidance in predicting which pmt enzymes are responsible for glycosylating a protein.

2. At the time of the present invention, it had further been demonstrated that glycosylation has no affect at all on the activity of AFP when expressed in rye grass. The reference of Pudney (Archives of Biochemistry and Biophysics 410: 238-245, 2003)

demonstrates that modulating the glycosylation of AFP in rye grass had no effect on the functional activity of the AFP. Accordingly, one skilled in the art could only interpret the results of this study to conclude that glycosylation is not significant in affecting the successful production and function of AFP.

3. At the time of the present invention, it was also unknown what effect glycosylation would have on a protein expressed in yeast. The reference of Sanders (J. Cell Biol. 145: 1177-1188, 1999, filed later than that of Ng) discloses that glycosylation is required for the stability and function of a protein produced in yeast. Accordingly, one skilled in the art would not have expected that obliterating glycosylation of AFP would actually improve the functional activity of the AFP.

Further, one skilled in the art would be inclined to dismiss the Ng reference for at least two reasons: 1) Ng discloses that modulating glycosylation is useful if the protein is experiencing mis-folding in yeast, and Chapman demonstrates, that this was not the case with the type III AFP; and 2) it was known in the art that modulating the glycosylation of a protein exerted unpredictable effects.

It is therefore submitted that one skilled in the art could not have arrived at the claimed invention based on the cited references. The references of Pudney and Chapman demonstrate that glycosylated type III AFP function perfectly in yeast. The reference of Ng is therefore inapplicable to the type III AFP. Moreover, type III AFPs had been reported in the art to be unaffected by glycosylation. Even further, one skilled in the art would not know which glycosylation enzymes to target in yeast for obtaining reduced glycosylation of type III AFP. Accordingly, Applicants submit that the claimed invention has been demonstrated to be overwhelmingly non-obvious, unexpected, and surprising in the art. It is therefore respectfully requested that this rejection be withdrawn.

Double-Patenting

The Advisory Action did not mention whether the prior rejection based on double-patenting would be maintained. In any event, Applicants submit that claims 1, 6-7, 8, 12, and 14-17 cannot be rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-9 of US Patent 7,297,516 in view of Ng and

Gentzsch 1.

US Patent 7,297,516 is the patent issued from the US national stage application of Chapman. The deficiencies of Chapman, Ng, and Gentzsch 1 are discussed herein and in arguments previously presented on the record. Accordingly, for the same reasons as discussed above, it is submitted that the claimed invention is not obvious over these cited references. It is therefore respectfully requested that this rejection also be withdrawn.

Conclusion

The foregoing amendments and remarks are thought to obviate the basis for the Examiner's rejections and to otherwise place the application in condition for allowance. Accordingly, Applicants respectfully request reconsideration and allowance of the pending claims. Should an interview be helpful to further prosecution of this application, the Examiner is invited to telephone the undersigned.

If there are any additional fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-0310. If a fee is required for an extension of time under 37 C.F.R. §1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,
Morgan, Lewis & Bockius LLP

/Zachary Derbyshire/

Zachary E. Derbyshire, Ph.D.
Registration No. 64,669

Dated: **February 23, 2010**
Morgan, Lewis & Bockius LLP
Customer No. **09629**
1111 Pennsylvania Avenue, N.W.
Washington, D.C. 20004
202-739-3000